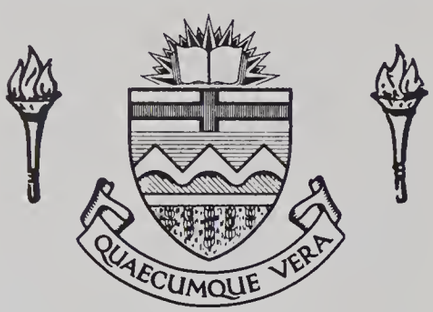

T H E U N I V E R S I T Y O F A L B E R T A

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THE UNIVERSITY OF ALBERTA

I. A PRACTICAL SYNTHESIS OF CIS-JASMONE

II. SYNTHETIC STUDIES ON NEPETALACTONE AND RELATED TERPENOIDS

by

JAMES ANDREW BULAT

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 1976

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

I. A PRACTICAL SYNTHESIS OF CIS-JASMONE

II. SYNTHETIC STUDIES ON NEPETALACTONE AND RELATED TERPENOIDS

submitted by James Andrew Bulat in partial fulfilment of the requirements for the degree of Master of Science.

TO MY MOTHER AND FATHER

ABSTRACT

Chapter I

A practical synthesis of cis-jasmone (1) has been achieved in six steps and an overall yield of 49%, starting from levulinic acid. Condensation of levulinic acid with ethylene glycol afforded ketal-ester 3. Reduction of 3 with lithium aluminium hydride gave ketal-alcohol 5 which was oxidized with Collin's reagent to yield ketal-aldehyde 6. Reaction of 6 with cis-3-hexenyl magnesium bromide gave ketal-alcohol 8 which was oxidized with Jones reagent giving dione 2, the immediate precursor of cis-jasmone (1). Final cyclization of 2 under basic conditions gave cis-jasmone (1).

Chapter II

A stereoselective synthesis of two potential synthetic precursors (keto-ester 27 and ketone 29) of nepetalactone (6) and related cyclopentanoids, 8 and 9 has been achieved. The synthesis demonstrates a new and efficient method for the construction of a functionalized bicyclo[3.3.0]octane system. It involves basically the formation of a suitably substituted bicyclo[3.2.0]heptane intermediate by photochemical means followed by the enlargement of its cyclobutane ring.

Photocycloaddition of 4-acetoxy-2-cyclopenten-1-one (12) to 1-propenyl acetate gave photoadduct 13. Acid catalyzed elimination of 13 yielded enone 14 which was subsequently treated with dimethyl lithium cuprate to give keto-ester 15. Hydrolysis of 15 followed by the removal of the ketone carbonyl afforded alcohol 22. Its oxidation to ketone 23 was accomplished in two different ways. Upon treatment with ethyl diazoacetate in the presence of boron trifluoride etherate, 23 underwent ring expansion smoothly to give keto-ester 27. Acid catalyzed decarbethoxylation of keto-ester 27 resulted in the formation of ketone 29.

ACKNOWLEDGEMENTS

The author extends his deepest gratitude to his research director, Dr. H. J. Liu, for constant encouragement and advice throughout this work. Dr. Liu was always available for discussion and seldom failed to introduce new and interesting ideas at those times.

The author wishes to thank the technical staff members of the Department of Chemistry, especially Dr. T. Nakashima and Mr. R. N. Swindlehurst and their associates for recording the nmr spectra, Dr. A. M. Hogg and his staff for recording the mass spectra and Mrs. D. Marlow and Mrs. A. Dunn for determining the microanalyses.

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INTRODUCTION

cis-Jasmone (1) the primary odorous principle of the flower oils of several varieties of Jasmin[1], is an important ingredient in both the production of high grade fragrances in the perfume industry[2,3] and as an enhancing agent for spearmint and peppermint flavors in the food industry[2,3]. It was first isolated from the essential oil of Jasmin grandiflorum and shown to be a ketone of chemical formula $C_{11}H_{16}O$ by Hesse[4] in 1899. Thirty years later its correct gross structure of 3-methyl-2-(2'-pentenyl)-2-cyclopenten-1-one was proposed independently by Ruzicka and Pfeiffer[5] and by Treff and Werner[6] on the basis of their degradative studies. The stereochemistry of the olefinic side chain, however, remained unsettled until 1952 when Crombie and Harper[7] prepared cis-jasmone (1) unequivically from cis-3-hexen-1-ol.

Because of its commercial importance and limited availability from natural sources as well as its unique structural features among naturally occuring compounds, cis-jasmone (1) has drawn much attention to its synthesis* in the last few decades. Many of the existing syntheses are concerned with the development of new/or improved methods for the construction of 1,4-diketones and cyclopentenones, using cis-jasmone (1) only as a testing model for their applicability. Often these procedures, as well as being lengthy, require costly and less available chemicals, thus they are not economically viable for the large scale production of cis-jasmone (1). Consequently there is a continuous demand for effective syntheses of cis-jasmone (1) using readily accessible and inexpensive materials.

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*For synthetic works prior to 1974, see references 8 and 9, and subsequent syntheses references 10-17.

Towards this end, levulinic acid* appears to be an ideal starting material. In addition to its being inexpensive and readily available, it could conceivably be converted into cis-8-undecene-2,5-dione 2, the known synthetic precursor of 1, by simple modification of the existing functionalities.

The first part of this thesis describes a practical synthesis of cis-jasmone (1) from levulinic acid in six stages and in an overall yield of 49%.

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*The use of levulinic acid and its derivatives for the synthesis of 1 via different routes has been reported concurrently with the present work as follows: while this work was in progress, Ho et al.[18], described their synthesis using levulonitrile as the starting material. Following the completion of this work the synthesis by Pattenen and Storer[12] starting from levulinic acid appeared and Heathcock and co-workers[13] reported a synthesis from methyl levulinate.

RESULTS AND DISCUSSION

Prior to the modification of the carboxyl group of levulinic acid, its more reactive ketone carbonyl was first protected. Treatment of levulinic acid with an excess of ethylene glycol in benzene in the presence of a catalytic amount of p-toluenesulfonic acid resulted in concomitant ketalization and esterification to give ketal-ester 3 in 87% yield. The structural assignment follows clearly from its spectral data. The infrared (ir) spectrum shows the characteristic hydroxyl group and ester carbonyl absorption bands at 3445 and 1725 cm^{-1}, respectively. In the nuclear magnetic resonance (nmr) spectrum the four methylene protons of the ketal group resonate at δ 3.89 as a singlet.

Reduction of ketal-ester 3 with an excess of lithium aluminium hydride gave rise to an 84% yield of ketal-alcohol 4. Its ir spectrum exhibits a strong absorption band at 3415 cm^{-1} for the hydroxyl moiety and the complete absence of any carbonyl absorption. Its mass spectrum displays no molecular ion peak but a very prominant signal at 131.0706 which is in agreement with the loss of a methyl group (calcd for $C_6H_{11}O_3$: 131.0708)*. Such a fragmentation pattern (the loss of an alkyl chain to give a stable oxonium ion) was found by Marshall and Williams[19] and others[20] to be consistent for 2,2-dialkyl dioxolanes. Ketal-alcohol 3 has previously been prepared by Brown and Dahl[21] using different routes and noted to be sensitive to acid which induces its rapid intramolecular transketalization to give cyclic ketal 5. In our hands, however, no appreciable deterioration of 4 was observed when it was properly stored at 0° with complete exclusion of acid.

Subsequent oxidation of 4 using Collins reagent[22] prepared

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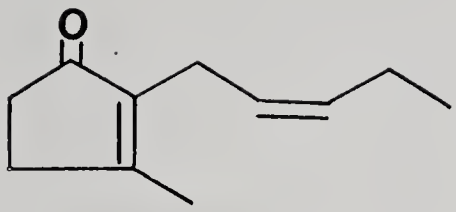
*Similarly, ketal-ester 3 did not exhibit a molecular ion peak (calcd for $C_9H_{16}O_5$: 204) in its mass spectrum but an intense peak at 189.



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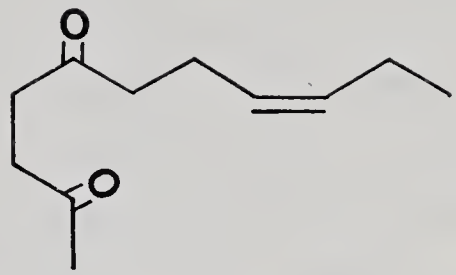

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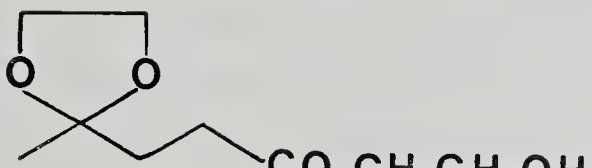

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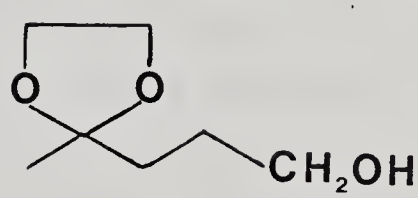

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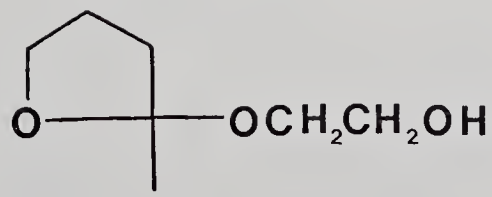

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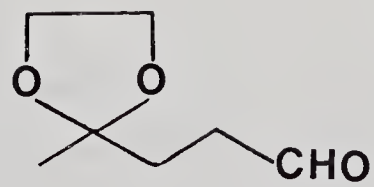

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in situ[23] gave rise to a 92% yield of ketal-aldehyde 6 whose ir and nmr spectral data were found to be in good agreement with those reported previously[21]. Instead of the expected molecular ion signal at 144, its mass spectrum displayed prominent peaks at 129 (the normal loss of a CH_3 unit) and 145 (presumably a protonated species). The ketal-aldehyde 6 proved to be very unstable. Its purification by either column chromatography or distillation could not be achieved without substantial loss of the material. The instability was further indicated by the fact that when 6 was exposed to chlorinated solvent for two days at 0° it was converted near quantitatively to keto-acetal 7* as a consequence of transketalization. In as much as the "crude" 6 was shown by both glc and tlc to be homogeneous, it was suitable for further transformation without purification.

The conversion of ketal-aldehyde 6 into dione 2, the well established precursor of *cis*-jasmone (1)[24], was carried out in two stages. Grignard reaction of 6 with *cis*-3-hexenyl magnesium bromide in ether gave rise to ketal-alcohol 8 which was found to be unstable and without purification was immediately treated with Jones reagent[25] which affected simultaneously its deketalization and oxidation to give dione 2 in a 90% yield. The ir and nmr spectra were shown to be identical with those previously reported[26]. The structure was further confirmed by its mass spectrum displaying a molecular ion peak at 182.1308 (calcd for $C_{11}H_{18}O_2$: 182.1306).

Final cyclization of dione 2 under the described conditions[26]

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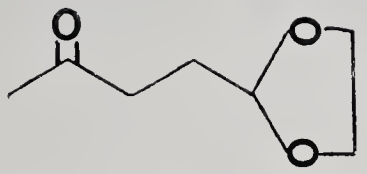
*The structure of 7 was evident from its spectral data. In the ir spectrum the absence of aldehyde absorptions at 2820, 2720 and 1720 cm^{-1} was coupled with the appearance of a new carbonyl absorption band at 1710 cm^{-1} whereas in the nmr spectrum a triplet at δ 9.40 for the aldehydic proton and a methyl singlet at δ 1.14 and 2.87 previously observed for ketal-aldehyde 6 shifted substantially to δ 4.78 and 2.87 readily accounted for by the methine proton of the acetal group and the three hydrogen atoms of the methyl ketone, respectively.



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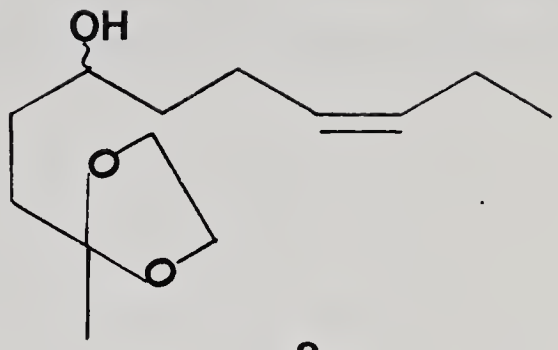

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resulted in the formation of cis-jasmone (1) in an 81% yield. Thus a total synthesis of cis-jasmone (1) from levulinic acid was achieved in a total yield of 49%. The nmr[14], ir[7], mass spectra[27], and the 2,4-DNP derivative[28] of the synthetic material were found to be identical with those described in the literature.

EXPERIMENTAL

General

Elemental analyses were performed by the microanalytical laboratory of this department. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared spectra (ir) were recorded on a Perkin-Elmer Model 337 or 457 grating infrared spectrophotometer. The spectra were calibrated using the 1601.4 cm^{-1} band of polystyrene. Nuclear magnetic resonance (nmr) were recorded on a Varian Associates Model A50/60 spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used in the text: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Mass spectra were recorded on a AEI Model MS-2 or MS-9 mass spectrometer.

Gas chromatograph analyses (glc) were performed using a Hewlett-Packard research chromatograph Model 5750 with a column of 15% SE 30 on Chromosorb W, 80 - 100 mesh.

Material

Levulinic acid (95%) purchased from the Aldrich Chemical Company was used without further purification. cis-1-Bromo-3-hexene was prepared from cis-3-hexen-1-ol (Aldrich Chemical Company) according to the reported procedure[26].

2-Hydroxyethyl-4,4-ethylenedioxypentanoate (3)

To a solution of 50 g (0.43 mol) of levulinic acid in 500 ml of benzene was added 200 g (3.22 mol) of ethylene glycol and 1 g (0.005 mol) of p-toluenesulfonic acid monohydrate. The resulting mixture was refluxed with a Dean-Stark water separator under a nitrogen atmosphere for 24 hr. Benzene was partially (ca. 200 ml) removed by distillation and the remaining mixture after cooling to room temperature

was poured into 300 ml of ice-cold saturated aqueous sodium bicarbonate. The combined aqueous solution was extracted with chloroform (4 x 300 ml) which was washed with saturated aqueous sodium chloride (250 ml). The organic solutions were combined, dried ($MgSO_4$), filtered, and concentrated. The oily product was distilled at 90-92°/0.05 mm to give 76.35 g (87%) of 3: nmr (CCl_4) δ 1.27 (s, 3 H, CH_3-), 1.97 (t, 2 H, J = 7 Hz, -CH_2CH_2C=O), 2.34 (t, 2 H, J = 7 Hz, -CH_2C=O), 3.31 (s, 1 H, -OH), 3.68 (t, 2 H, J = 6.5 Hz, -CH_2OH), 3.89 (s, 4 H, -OCH_2CH_2O-), and 4.11 (t, 2 H, J = 6.5 Hz, -CH_2CH_2OH); ir (film) ν 3445 (alcohol) and 1725 cm^{-1} (ester).

Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 53.01, 52.67; H, 7.91, 7.78.

4,4-Ethylenedioxypentan-1-ol (4)

At 0°, a solution of 40.8 g (0.2 mol) of ketal-ester 3 in ether (250 ml) was added dropwise over a 1.5 hr period to a suspension of lithium aluminium hydride (10 g; 0.26 mol) in 150 ml of ether. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 16 hr. After cooling to 0°, ethanol and water were added sequentially to destroy excess lithium aluminium hydride. The organic layer was separated and the aqueous solution extracted with ether (3 x 500 ml) and chloroform (2 x 500 ml). The combined organic solution was dried over magnesium sulfate, filtered and concentrated. The crude oil after distillation at 62-64°/0.04 mm gave a 24.5 g (84%) yield of 4: nmr (CCl_4) δ 1.26 (s, 3 H, CH_3-), 1.63 (m, 4 H, -$CH_2CH_2CH_2OH$), 3.40-3.62 (m, 2 H, -CH_2OH), 3.75 (s, 1 H, -OH), and 3.88 (s, 4 H, -OCH_2CH_2O-); ir (film) ν 3415 cm^{-1} (alcohol); mass spectrum: m/e (M - 15) 131.0706 (Calcd for $C_6H_{11}O_3$: 131.0708).

Anal. Calcd for $C_7H_{14}O_3$: C, 57.53; H, 9.65. Found: C, 57.71; H, 9.66.

4,4-Ethylenedioxypentanal (6)

The oxidation was carried out using the procedure of Ratcliffe and Rodehorst[23].

Chromium trioxide (60 g; 0.6 mol) was added to a stirred solution of pyridine (94.9 g; 1.2 mol) in 1200 ml of methylene chloride under a nitrogen atmosphere at 0°. The resulting mixture was warmed to room temperature and stirred for an additional 15 min. At the end of this period, a solution of ketal-alcohol 4 (14.6 g; 0.1 mol) in 50 ml of methylene chloride was added in one portion. The mixture was stirred at room temperature for 20 min and then 300 ml of water was added. The methylene chloride solution was separated and the aqueous phase extracted with methylene chloride (3 x 300 ml). The organic extracts were washed successively with the following ice-cold solutions: 2 N sodium hydroxide (500ml), 2 N hydrochloric acid (2 x 500 ml), saturated aqueous sodium bicarbonate (500 ml), and water (500 ml). Drying over magnesium sulfate, filtration and concentration gave 13.2 g (92%) of 6 which was shown to be homogeneous by tlc and glc. An analytical sample was obtained by Kugelrohr distillation at an oven temperature of 50°/ 2.5 mm to give the following spectral data: nmr (benzene-d_6) δ 1.14 (s, 3 H, CH_3-), 1.67-2.20 (m, 4 H, -$\underline{CH}_2\underline{CH}_2$CHO), 3.50 (s, 4 H, -$OCH_2CH_2O$-), and 9.42 (t, 1 H, J = 2 Hz, -CHO); ir (film) ν 2880, 2720 and 1720 cm^{-1} (aldehyde).

cis-8-Undecene-2,5-dione (2)

To a stirred suspension of 486 mg (20 g-atom) of magnesium turnings in 25 ml of ether containing a catalytic amount of methyl iodide (1 drop) was added dropwise, a solution of 3.26 g (20 mmol) of cis-1-bromo-3-hexene in 5 ml of ether, over a 1 hr period. After stirring at room temperature for an additional 1 hr, ketal-aldehyde 6 (2.16 g; 15 mmol) was added dropwise over a period of 20 min. Stirring was continued for an additional 30 min and then methanol and water were added. The resulting mixture was extracted with chloroform (4 x 50 ml) and washed with saturated aqueous ammonium chloride (50 ml) and saturated aqueous sodium chloride (50 ml). The chloroform solution after drying over magnesium sulfate was filtered and concentrated to yield 3.37 g of 2,2-ethylenedioxy-8-undecen-5-ol (8) which was found to be unstable and was used in the ensuing reaction without purification.

To a solution of 2.5 g (1.1 mmol) of 8 in 75 ml of acetone at 0° was added 50 ml of 8 N Jones reagent[25] dropwise, over a period of 30 min. The resulting mixture after stirring for an additional 1.5 hr was poured into 100 ml of water and extracted with chloroform (4 x 100 ml). The chloroform solution was dried ($MgSO_4$), filtered and concentrated to give an oil which was subjected to silica gel column chromatography. Elution with a solution of 5% ether in benzene gave 1.82 g (90% from 6) of 2: nmr ($CDCl_3$) δ 0.95 (t, 3 H, J = 7 Hz, CH_3CH_2-), 1.82-2.48 (m, 6 H, $-COCH_2CH_2CH{=}CHCH_2-$), 2.15 (s, 3 H, CH_3CO-), 2.67 (s, 4 H, $-COCH_2CH_2CO-$), and 5.33 (m, 2 H, -CH=CH-); ir (film) ν 1715 c cm^{-1} (ketone); mass spectrum: M^+ 182.1308 (Calcd for $C_{11}H_{18}O_2$: 182.1306).

cis-Jasmone (1)

A solution of 1.10 g (6 mmol) of the diketone 2 in 3 ml of 95% ethanol and 10 ml of 0.5 N sodium hydroxide was refluxed under a atmosphere of nitrogen for 5 hr. The reaction mixture was cooled to room temperature and extracted with chloroform (4 x 100 ml). The chloroform solution was washed with saturated aqueous sodium chloride, dried over magnesium sulfate, filtered, and concentrated. Column chromatography of the oily product on silica gel, using a solution of 5% ether in benzene as eluent gave 800 mg (81%) of cis-jasmone (1): nmr ($CDCl_3$) δ 0.96 (t, 3 H, J = 7.5 Hz, CH_3CH_2-), 2.03 (s, 3 H, $CH_3C{=}$), 2.83 (d, 2 H, J = 5.5 Hz, $-CH_2CH{=}$), and 5.20 (m, 2 H, -CH=CH-); ir (film) ν 1685 (conjugated ketone) and 1645 cm^{-1} (double bond); mass spectrum: M^+ 164.1197 (Calcd for $C_{11}H_{16}O$: 164.1201); 2,4-DNP: mp 118° (literature[28] 117.5°).

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INTRODUCTION

The photochemical cycloaddition of a conjugated enone to an olefin producing a cyclobutane ring has been known since the turn of the century, owing to the work of Ciamician and Silber[1], on the photoisomerization of carvone (1) and carvonecamphor (2). For the next fifty years, however, the field of photocycloaddition reactions remained relatively dormant; only a few reactions were reported[2] and those were concerned exclusively with intramolecular processes. Buchi and Goldman's[3] reinvestigation of Ciamician's work on carvone (1) in the late 1950's, revived interest in this field. The scope of the reaction quickly extended to intermolecular processes, studied independently by de Mayo[4] and Eaton[5]. The application of these reactions to synthetic organic chemistry has allowed the direct construction of highly strained cyclobutane ring containing compounds as well as by subsequent modifications of the resulting cyclobutane rings[6,7], useful organic systems which are otherwise accessible only with great difficulty.

Recently a facile synthesis of hydrindanonecarboxylates has been achieved in this laboratory[8] involving initial construction of bicyclo[4.2.0]octan-7-ones using the photocycloaddition reaction as a general entry and subsequent ring expansion of the cyclobutanone moiety with ethyl diazoacetate[9-14] in the presence of boron trifluoride etherate as a catalyst. For example[8], irradiation of isophorone and vinyl acetate resulted in the formation of photoadduct 3 which upon treatment with hydrazine and potassium hydroxide under Wolff-Kishner reaction[15,16] conditions followed by Jones oxidation[17] of the reduction product gave rise to cyclobutanone 4. The ring expansion of 4 with ethyl diazoacetate in the presence of boron trifluoride etherate yielded hydrindanone-carboxylate 5. This general synthetic approach also demonstrated for the first time the direct transformation of cyclobutanones to their next higher homologs, in excellent yield*. The ring expansion reaction was

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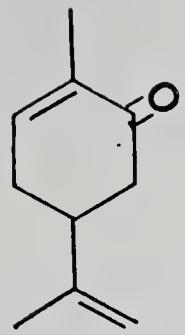
*Concurrent to this work Schleyer, et al.[14] have also reported an isolated case wherein a cyclobutanone ring was expanded to a five membered one.



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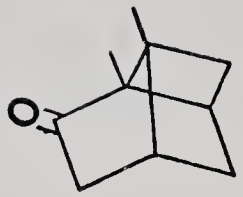

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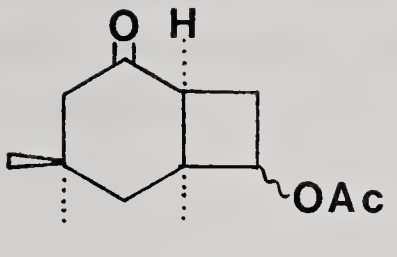

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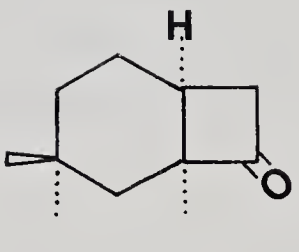

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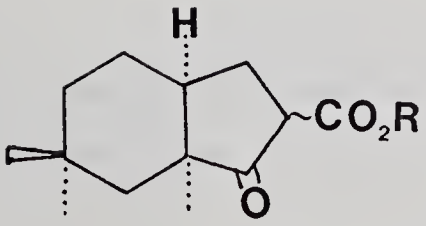
Ac = CH_3CO_2–



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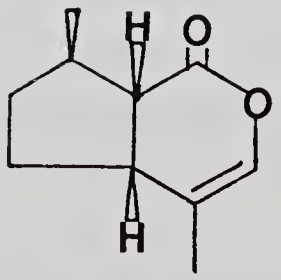

6

R = C_2H_5–

found to be highly regioselective[18] in cases of unsymmetrically substituted ketones. In all the cases studied, the migratory appitude was shown to be such that in contrast to the known rearrangement reactions[19] the less substituted carbon migrates exclusively*.

A logical extension of this synthetic approach would be, within the limitations** of the photocycloaddition reaction, the investigation of its applicability to the synthesis of bicyclo[n.3.0] systems starting with a cyclic enone of adequate ring size. Of particular interest are the bicyclo[3.3.0] systems. There is considerable general interest in these compounds as they are potentially useful intermediates in the synthesis of natural products possessing a skeleton in which two or more five-membered rings are fused, e.g. those of the hirsutane and the capnellane families, or they could be derived from such by skeletal modifications. As a consequence, we have undertaken studies on the applicabliity of such a scheme towards the synthesis of a bicyclo[3.3.0]octane system using nepetalactone (6) as a target molecule.

Nepetalactone (6) is a major constituent of the essential oil of the catmint plant, Nepta cataria and a representative member of a class of cyclopentanoid monoterpenes[21,22] possessing the general carbon skeleton 7. Its structure was elucidated independently by McElvain[23-27] and Meinwald[28] in the mid-1950's and since then two independent syntheses have been reported[29-31].

Two lactones, iridomyrmecin (8) and isoiridomyrmecin (9) which are closely related to nepetalactone (6) in structure have also been isolated from a variety of natural sources (Iridomyrmex humilis Mayr.[32];

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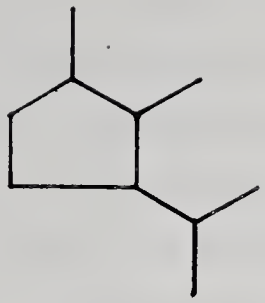
*The same migratory appitude was found to be consistant as well in cyclic ketones[18] other than cyclobutanone.

**For instance, it has been shown[20] that irradiation of 2-cycloheptanone or 2-methyl-2-cyclohexanone with an olefin does not yield clean cycloaddition product.



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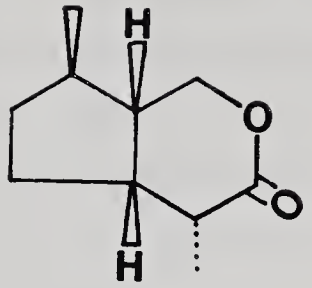

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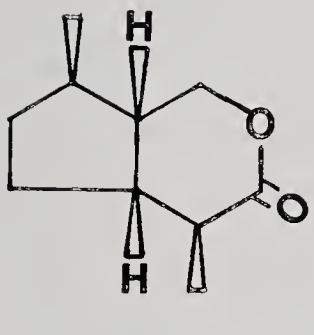

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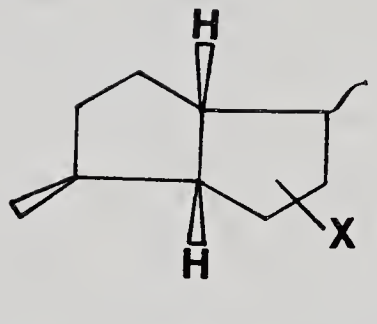

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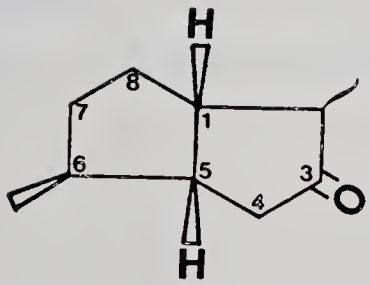

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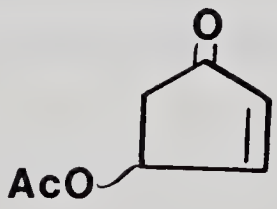

12

Iridomyrmex nitidus Mayr.[33]; Actinida polygama[34,35]). Both compounds were shown to have interesting insecticidal and antibiotic activities[36]. By virtue of the structural similarities[37-39] of these three naturally occurring lactones, it is quite conceivable that a functionalized bicyclic compound such as 10 (X = functional group) could serve as a common intermediate for their synthesis with suitable modifications, i.e. oxidative cleavage of the functionalized cyclopentane and lactonization. In fact the validity of such a scheme has been demonstrated by Sakan and co-workers[30] who achieved the synthesis of these lactones* using 2,6-dimethylbicyclo[3.3.0]octan-3-one (11) as an intermediate.

With this in mind, we have chosen at the outset of the present work a compound of type 10 as the first synthetic target. Towards this end, it is highly desirable to incorporate the two required methyl groups at an early stage with good stereochemical control. Strategically target molecule 10 would be prepared by ring expansion of a bicyclo[3.2.0] system, which in turn would be formed by fusing photochemically a cyclopentenone and an olefin, a careful selection of these two starting materials could fulfill such a requirement. It is anticipated that 4-acetoxy-2-cyclopenten-1-one (12) would provide an adequately activated site for the purpose of incorporating the C-8 methyl group at an early stage whereas the use of 1-propenyl acetate would allow direct introduction of the C-4 methyl group.

The second part of this thesis describes an efficient synthesis of two potential synthetic precursors of the aforementioned naturally occurring lactones whereby it illustrates a new approach to the functionalized bicyclo[3.3.0]octane ring system.

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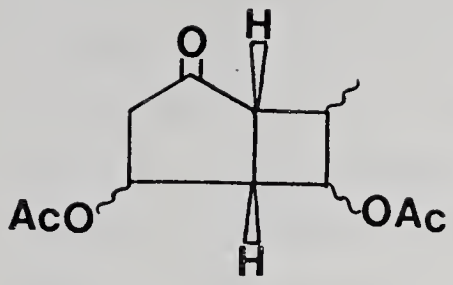
*For other syntheses of iridomyrmecin (8) and isoiridomyrmecin (9) see ref. 40-44.

RESULTS AND DISCUSSION

4-Acetoxy-2-cyclopenten-1-one (12) and 1-propenyl acetate, the two counterparts of the initiating photocycloaddition reaction, were prepared according to the procedures of DePuy et al.[45-47] and Curtin and Hurwitz[48], respectively, with some modifications. A 3:2 mixture of the two geometric isomers of 1-propenyl acetate was obtained and used without separation.

Irradiation of a solution of (12) with an excess of 1-propenyl acetate in benzene for 24 hours gave rise to a diastereomeric mixture of photoadduct 13. The photocycloaddition reaction proceeded with a high degree of regioselectivity in the expected head-to-tail manner. The orientation of the products follows clearly from further transformations. Photoadduct 13 was found to undergo a favorable elimination reaction upon prolonged exposure to Kiesegel[49], in an attempt to purify it, giving the desired product enone 14. More effectively 14 could be obtained by treatment of 13 with a small amount of p-toluenesulfonic acid in benzene. Enone 14 thus obtained in a 54% yield from 12 was shown to be a diastereomeric mixture consisting of at least three stereoisomers as indicated by its nmr spectrum which exhibited three doublets at δ 0.90, 1.10 and 1.35 for the C-7 methyl group as well as three singlets at δ 1.97, 1.99 and 2.08 for the acetoxy group. The ir spectrum showed absorption bands at 1736, 1701 and 1574 cm^{-1} for the ester and the ketone carbonyls and the double bond,respectively. The ketone absorption appeared at a somewhat lower than normal value[50] but it was found to be general in cases in which a cyclic ketone is fused to a four-membered ring. Since two of the four chiral centers present in 14 will be either destroyed or possibly epimerized in the later stages, no attempt was made to separate these isomers.

The incorporation of a methyl group into the C-4 position of enone 14 was subsequently affected by a 1,4-addition reaction. Treatment of 14 with dimethyl lithium cuprate under standard conditions[51] gave



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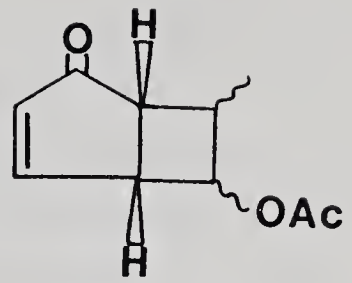

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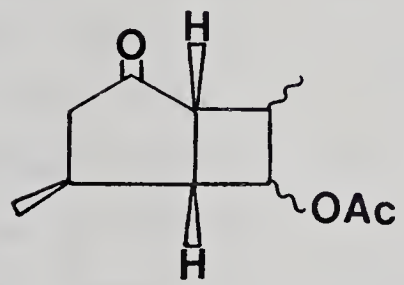

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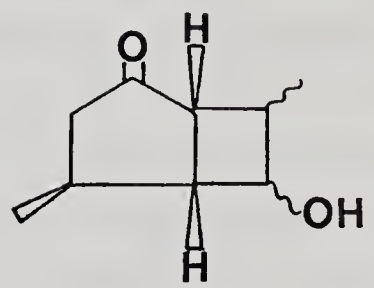

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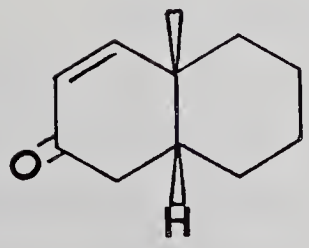

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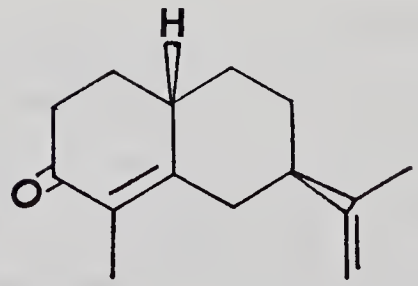

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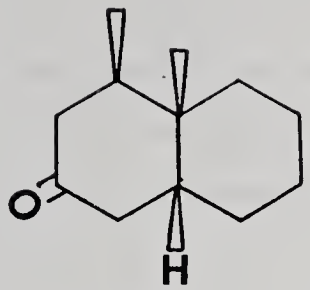
in addition to 7% recovered starting material 14, a 67% yield of acetate 15 (on the basis of consumed material) and a small amount (7%) of the corresponding alcohol 16. The structure of keto-ester 15 was evident from its spectral data. The ir spectrum showed the absence of conjugated enone absorption and an intense band at 1743 cm^{-1} for both the cyclopentanone and the ester functionalities. The nmr spectrum displayed additional methyl doublets in the δ 0.83-1.19 region and no signal above δ 5. Although the mechanistic[52] aspects of the 1,4-addition of organo "ate" complexes to enones remain to be ascertained and the development of a more sophisticated theory is necessary in order to account for the stereochemical outcome, a vast number of experimental results[51-55] strongly suggested, regardless whatever the mechanism maybe, that the addition proceeds predominately from the less hindered side of the molecule. For example[51,54], addition of dimethyl lithium cuprate to the bicyclo[4.4.0]octenones 17 and 18 gave exclusively the cis-decalones 19 and 20, respectively. On the basis of these findings, it is anticipated that the addition of dimethyl lithium cuprate to enone 14 would proceed from the substantially less hindered vertex face and as a consequence the cis stereochemistry could readily be assigned for the newly incorporated methyl group and the ring junction hydrogens.

Prior to the removal of the ketone of 15, its acetoxy group was first hydrolyzed with saturated aqueous sodium carbonate in methanol to give keto-alcohol 16 in a 78% yield (57% from enone 14 in combination with 16 obtained in previous reaction).

The ketone carbonyl was then removed in two different ways. Treatment of keto-alcohol 16 with 1,2-ethanedithiol in the presence of boron trifluoride etherate resulted in the formation, in a 87% yield, of thioketal 21 whose ir spectrum exhibited a hydroxyl band at 3440 cm^{-1} and no carbonyl absorption. The ethylene group of the thioketal resonated at δ 3.19 as a singlet in the nmr spectrum. The mass spectrum showing a molecular ion peak at 230.0794 was in agreement with the structural assignment. Subsequently by boiling a solution of thioketal



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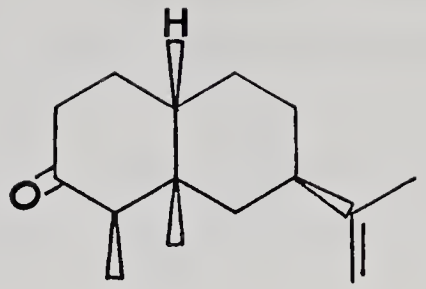

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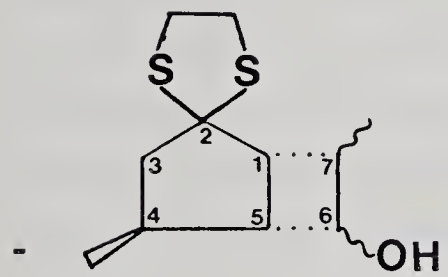

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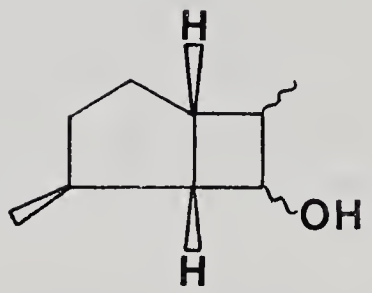

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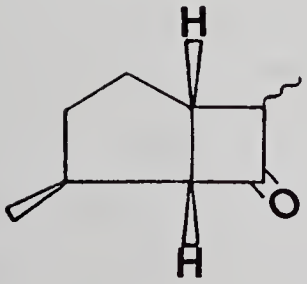

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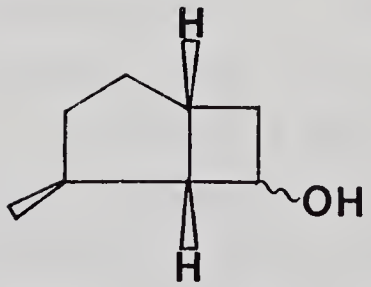

24

21 and W-2 Raney nickel[56] in ethanol for 24 hours affected its reduction to give alcohol 22 in an 80% yield. The complete removal of the thioketal signal was found to be absent. Alternatively the same compound 22 could be obtained directly from keto-alcohol 16 by Wolff-Kishner[15] reduction using Huang-Minlon's modification[16]. In spite of the reactions simplicity, however, the lower yield (61% vs 67% by the two step sequence) coupled with the fact that results were not completely reproducible made this approach less preferable.

The oxidation of alcohol 22 was likewise achieved via two different routes. Initially, Jones oxidation[17] was employed and ketone 23 was obtained. The ketone was found to be extremely volatile and its attempted purification resulted in substantial loss of material. Compound 23 of satisfactory purity (contaminated only by a small amount of the solvents used as shown by its nmr spectrum) could, however, be obtained in 83% yield, by distillation using a Kugelrohr apparatus. The nmr spectrum also indicated that ketone 23 consisted of two diastereomers* showing a total of four doublets in the methyl region.

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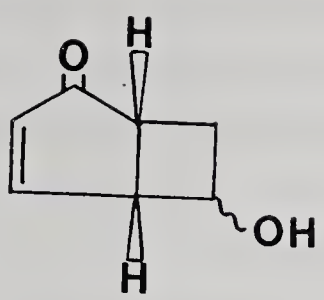
*On the following basis, the two diastereomers are most likely due to the chiral center of C-7 rather than that of C-4. It has been shown that both C-7 epimers must be present prior to the oxidation stage (e.g. 14 contained at least three diastereomers (vide supra)) and under the extremely mild Jones oxidation conditions total epimerization of this center is unlikely. Furthermore, the same diastereomeric ketones were also obtained from 22 using a modified Moffatt oxidation[57] (vide infra). In addition, recent investigation in this laboratory[58] showed that oxidation of alcohol 24 prepared by a similar route from 12 and vinyl acetate involving at one stage addition of dimethyl lithium cuprate to enone 25 gave rise to ketone 26 as a single compound. This finding requires that the addition reaction occurred with total stereoselectivity. It is highly conceivable that the addition of dimethyl lithium cuprate to the present closely related system would proceed in the same manner.



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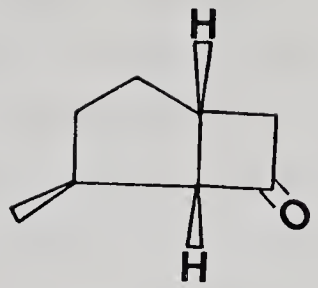

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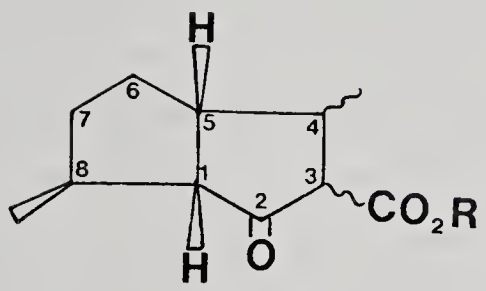

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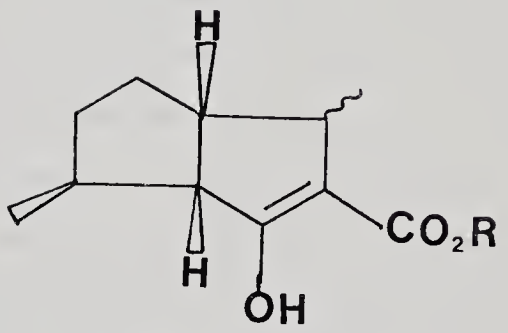
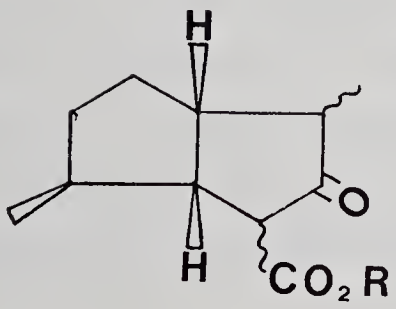


27a



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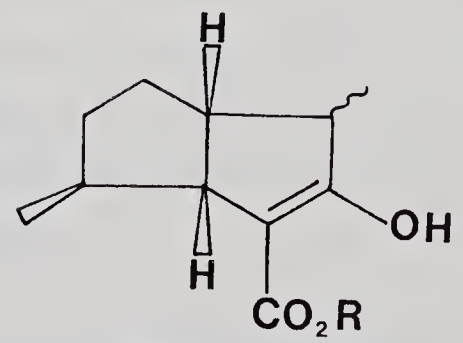
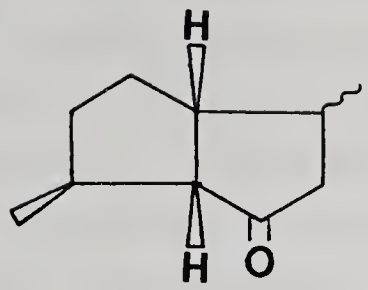


28a

The ir spectrum showing an absorption band at 1778 cm^{-1} diagnostic for cyclobutanone and the mass spectrum displaying a molecular ion peak at 138.10439 were consistant with the structure assigned. Recent investigations in this laboratory[58] showed that in cases of cyclobutanols the Moffatt oxidation is superior to the Jones oxidation. As a consequence, the oxidation of alcohol 22 by this method was investigated. Treatment of 22 with a mixture of dimethyl sulfoxide and acetic anhydride at fridge temperature (≈3°) for two days gave rise to a slightly improved yield (≈88%) of ketone 23. This ketone was found to be identical spectroscopically and chromatographically with that previously obtained. It was also contaminated by traces of solvents as shown by its nmr spectrum.

The conversion of ketone 23 into the desired bicyclo[3.3.0] octane system proceeding the synthesis of nepetalactone (6) and/or related terpenes requires the insertion of one carbon unit into the existing cyclobutanone ring. This was achieved as originally conceived by the use of the method recently developed in this laboratory[14]. When 23 was treated with boron trifluoride etherate and ethyl diazoacetate in ether at -30° for 5 hours, the ring expansion occurred smoothly to give a 93% yield of β-keto ester(s) (27 and/or 28), existing in about 50% in the enol form (27a and/or 28a) in carbon tetrachloride solution as shown by the nmr spectrum: the two singlets appeared at δ 10.43 and 10.55 (due to stereoisomers and/or positional isomers) for the chelated enol protons and a multiplet at δ 4.28-4.53 for the methine proton adjacent to the carbonyls integrated to a ratio of 1:1. The ir spectrum showed to the cyclopentenone and the ester carbonyl absorptions at 1755 and 1729 cm^{-1}, respectively, absorption bands at 3440, 1658 and 1619 cm^{-1} characteristic[59] of the chelated β-hydroxy acrylate moiety. A molecular ion peak at 224.1404 observed in the mass spectrum further confirmed the gross structural assignment.

Although the gross structure of the ring expansion product(s) could be readily assigned spectroscopically without any difficulty and ambiguitity, the location of the ketone carbonyl and thus the ester grouping could not be defined at this stage due to the complication



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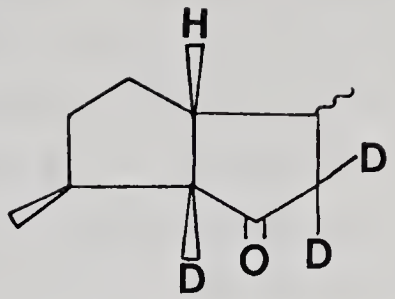


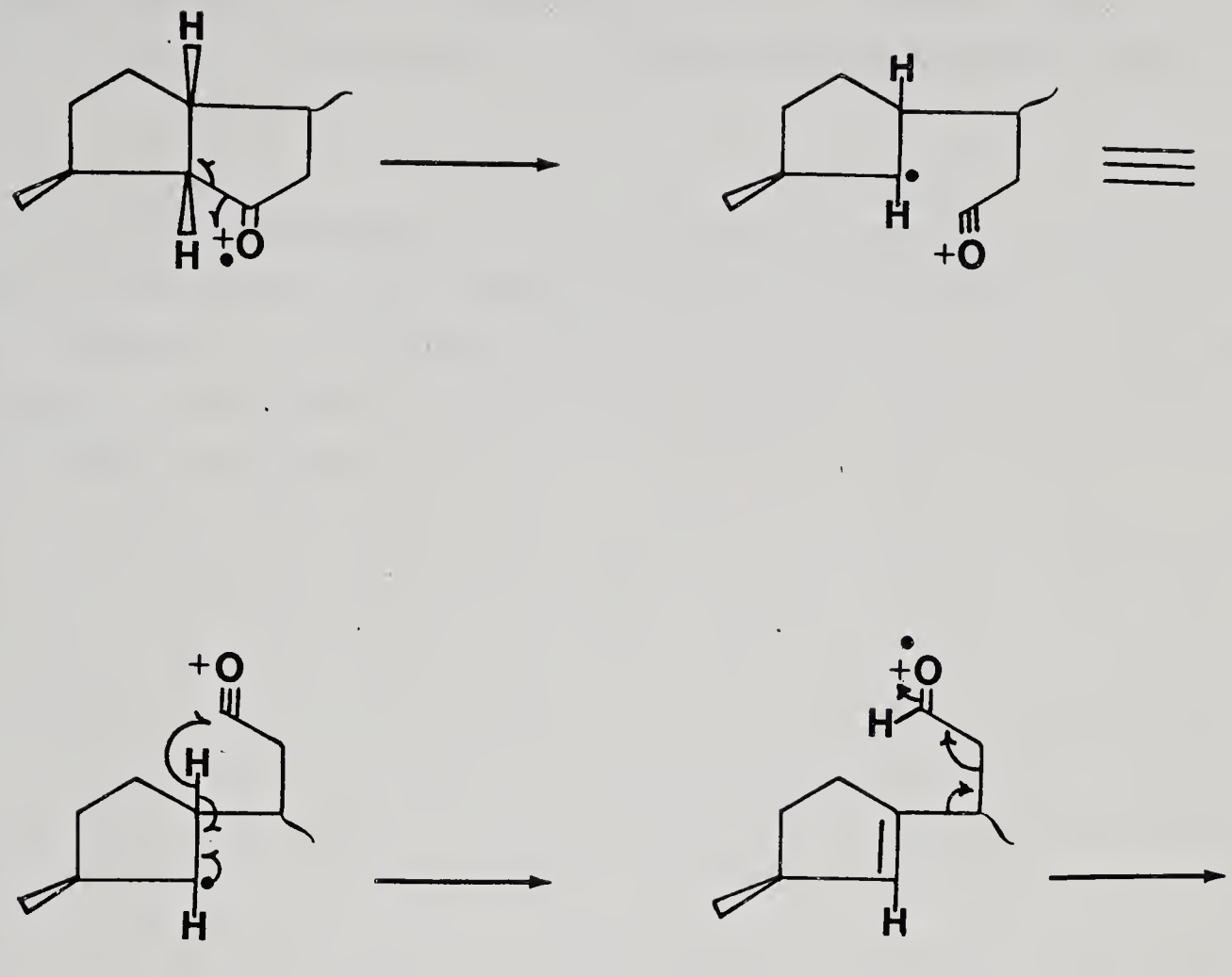
29a

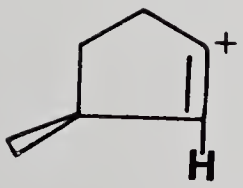
of keto-enol tautomerization as well as the coexisting isomers. This aspect was clarified in the following manner. Acid decarbethoxylation of the ring expansion product(s) gave rise to a near quantitative yield of bicyclic ketones which were identified to be a diastereomeric mixture of 29 as follows. The melting point (112-113°) of the 2,4-DNP derivative of the major isomer was found to be different from the corresponding derivative of 11 (with its stereochemistry unspecified) previously prepared by Sakan and co-workers[29], suggesting the differences in the locations of their ketone carbonyls. This evidence was inconclusive since neither the stereochemistry of 11 nor that of our compound was known.

Definite proof arose when the ring expansion product(s) was decarbethoxylated with deuterated sulfuric acid in methanol-d_4 and deuterium oxide. The mass spectrum of the product(s) showed that three deuteriums were incorporated to an extent of greater than 85% with the remaining in the dideuterated form. As in the case of the non-deuterated material both of the methyl groups appeared as doublets. This observation clearly indicated that the ketone carbonyl was to an exclusive extent "meta" to the C-4 methyl group, since should it be situated at a position "ortho" to the C-4 methyl group, the C-4 hydrogen is expected to undergo exchange with deuterium and replacing a hydrogen atom with deuterium at C-4 should result in the collapse of a methyl doublet into a singlet. Thus the structures of the decarbethoxylation products could be assigned as 29 and 29a and that of the precursors as 27.

The same conclusion was reached by further analysis of the mass spectra of the decarbethoxylation product(s). The non-deuterated ketone showed a base peak at 81.0705, corresponding to $C_6H_9^+$ whose structure could be rationalized as 30 by invoking the following fragmentation process[60,61].

Scheme I





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In the case of the deuterated material, the base peak appeared at 82.0763 accounted for by $C_6H_8D^+$. On the basis of the same fragmentation pattern the generation of this relatively stable ion required prior incorporation of a deuterium atom into the ring junction C-1.

The development of a new synthetic approach to the functionalized bicyclo[3.3.0]octane system of considerable interest as well as the preparation of keto-ester 27 and ketone 29 represents the current advance of our studies on the total synthesis of nepetalactone (6) and related compounds.

EXPERIMENTAL

General

Infrared and nuclear magnetic resonance spectra, melting points, elemental analyses, and glc were obtained and reported as indicated in the Experimental section of Part I. Mass spectra were recorded on an AEI Model MS-2, MS-9 or MS-50 mass spectrometer.

Material

Practical grade propionaldehyde was dried over magnesium sulfate for 14 hours and distilled (bp 48-49°/700 mm). Potassium acetate was dried for 14 hours at 260° prior to use. Dimethyl sulfoxide was freshly distilled from calcium hydride. Acetone was dried over calcium sulfate for 14 hours and distilled from potassium permanganate. Kiesegel, 0.15-0.33 mm granulation, was used as adsorbant for column chromatography.

2-Cyclopenten-1-one was prepared from a mixture of 3,4- and 3,5-cyclopentenediol (Research Organic/Inorganic Chemical Corp.) according to the procedure of DePuy and Eliers[45-47].

4-Acetoxy-2-cyclopenten-1-one (1)

This compound was prepared from 2-cyclopenten-1-one using the procedure of DePuy *et al.*[45] with modifications. A mixture of 2-cyclopenten-1-one (110 g; 1.3 mol), 98% N-bromosuccinimide (243 g; 1.3 mol) and 2,2'-azobis(2-methylpropionitrile) (0.5 g; 0.003 mol) in 1650 ml of carbon tetrachloride was heated on a steam bath for 1 hr. The mixture was then cooled to 0°, filtered and the residue washed thoroughly with ice cold carbon tetrachloride (3 x 200 ml). The filtrate was washed thoroughly with 1 N sodium thiosulfate (500 ml) and ice-water (3 x 350 ml), dried over magnesium sulfate, filtered, and concentrated to give crude 4-bromo-2-cyclopenten-1-one as a reddish-brown oil.

To a solution of this oily product (100 g; ca. 0.6 mol) in 1000 ml of glacial acetic acid, was added 103 g (0.61 mol) of silver acetate. The resulting mixture was stirred under a nitrogen atmosphere at reflux for 24 hr, filtered and the precipitate washed with glacial acetic acid (2 x 200 ml). Removal of the solvent in vacuo followed by distillation of the remaining oil at 46-48°/0.5 mm yielded 43 g (47%) of 1 as a colorless oil: ir (film) ν 1743 (ester), 1730 (ketone) and 1593 cm^{-1} (double bond); nmr (CCl_4) δ 2.04 (s, 3 H, CH_3CO-), 2.25 (dd, 1 H, J = 19 Hz, J' = 6 Hz, -C<u>H</u>(H)CO-), 2.71 (dd, 1 H, J = 19 Hz, J' = 3 Hz, -C<u>H</u>(H)CO-), 5.76 (dddd, 1 H, J = 6 Hz, J' = 3 Hz, J'' = 2 Hz, J''' = 1 Hz, -C<u>H</u>OCOCH$_3$), 6.23 (dd, 1 H, J = 6 Hz, J' = 1 Hz, -COCH=), and 7.52 (dd, 1 H, J = 6 Hz, J' = 2 Hz, -C<u>H</u>=CHCO-); mass spectrum M^+ 140.0476 (Calcd for $C_7H_8O_3$: 140.0474).

1-Propenyl Acetate

A modification to the procedure of Curtin and Hurwitz[48] was used to prepare 1-propenyl acetate. Propionaldehyde (627 g; 10.8 mol) was dissolved in 2300 ml (22.5 mol) of acetic anhydride and 1192 g (10.1 mol) of potassium acetate was added. The mixture was refluxed for 20 hr with vigorous stirring and the resulting solution was distilled and the fraction boiling between 114° and 127° was collected. The distillate was poured into ice-cold water and solid sodium carbonate was added slowly with vigorous stirring until the aqueous layer became slightly basic. The organic phase was separated and the aqueous solution was extracted with methylene chloride (3 x 200 ml). The combined organic solution was washed with water (250 ml), dried over magnesium sulfate, filtered, and concentrated. Distillation of the resulting oil yielded 307 g (28%) of 1-propenyl acetate as a mixture of two geometrical isomers: ir (film) ν 1755 (ester and 1675 cm^{-1} (double bond); nmr (CCl_4) δ 1.61 and 1.68 (both d, total 3 H, J = 2 Hz, C<u>H</u>$_3$CH=), 2.07 and 2.09 (both s, total 3 H, CH_3OCO-), 4.78 (m, 1 H, CH_3C<u>H</u>=), and 6.97 (m, 1 H, =C<u>H</u>OCOCH$_3$); mass spectrum M^+ 100.0525 (Calcd for $C_5H_8O_2$: 100.0524).

4,6-Diacetoxy-7-methylbicyclo[3.2.0]heptan-2-one (2)

The apparatus used for the photocycloaddition reaction is shown in Figure 1. A solution of 1-propenyl acetate (cis and trans mixture; 277 g; 2.8 mol) and 4-acetoxy-2-cyclopenten-1-one (1) (26 g; 0.18 mol) in 500 ml of dry benzene was irradiated for 12 hr at 0° and 12 hr at room temperature with a 450 W Hanovia high-pressure mercury lamp fitted with a pyrex filter. During the irradiation a constant stream of dry and oxygen free nitrogen was passed through the solution to facilitate its mixing. Concentration of the resulting solution under reduced pressure (20 mm) furnished 43 g of crude 2 as an oil.

6-Acetoxy-7-methylbicyclo[3.2.0]heptan-2-one (3)

The crude photoadduct 2 (43 g) and p-toluenesulfonic acid monohydrate (4.3 g) were dissolved in 200 ml of dry benzene and the solution was stirred at room temperature under a nitrogen atmosphere for 24 hr. The reaction mixture was made basic with ice-cold 1 N sodium bicarbonate. The benzene solution was seperated and the aqueous layer extracted with ether (3 x 100 ml). The organic extracts were washed with saturated aqueous sodium bicarbonate (250 ml) and water (250 ml), combined, dried ($MgSO_4$), filtered, and concentrated to give a brown oil which was distilled at 84-91°/0.4 mm giving 18 g (56% from 1) of 3: ir (film) ν 1736 (ester), 1701 (ketone) and 1574 cm^{-1} (double bond); nmr (CCl_4) δ 0.90, 1.10 and 1.35 (all d, total 3 H, J = 7 Hz, CH_3-), 1.97, 1.99 and 2.08 (all s, total 3 H, CH_3CO-), 2.14 (m, 1 H, $CH_3C\underline{H}$-), 2.91 and 3.70 (both m, 1 H each, -COCHCH-), 4.69 (m, 1 H, -$C\underline{H}OCOCH_3$), 6.25 (m, 1 H, =CHCO-), and 7.59 (m, 1 H, $C\underline{H}$=CHCO-); mass spectrum M^+ 180.0784 (Calcd for $C_{10}H_{12}O_3$: 180.0787).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.35; H, 6.99.

6-Acetoxy-4,7-dimethylbicyclo[3.2.0]heptan-2-one (4)

To a vigrously stirred suspension of cuprous iodide (17.5 g;

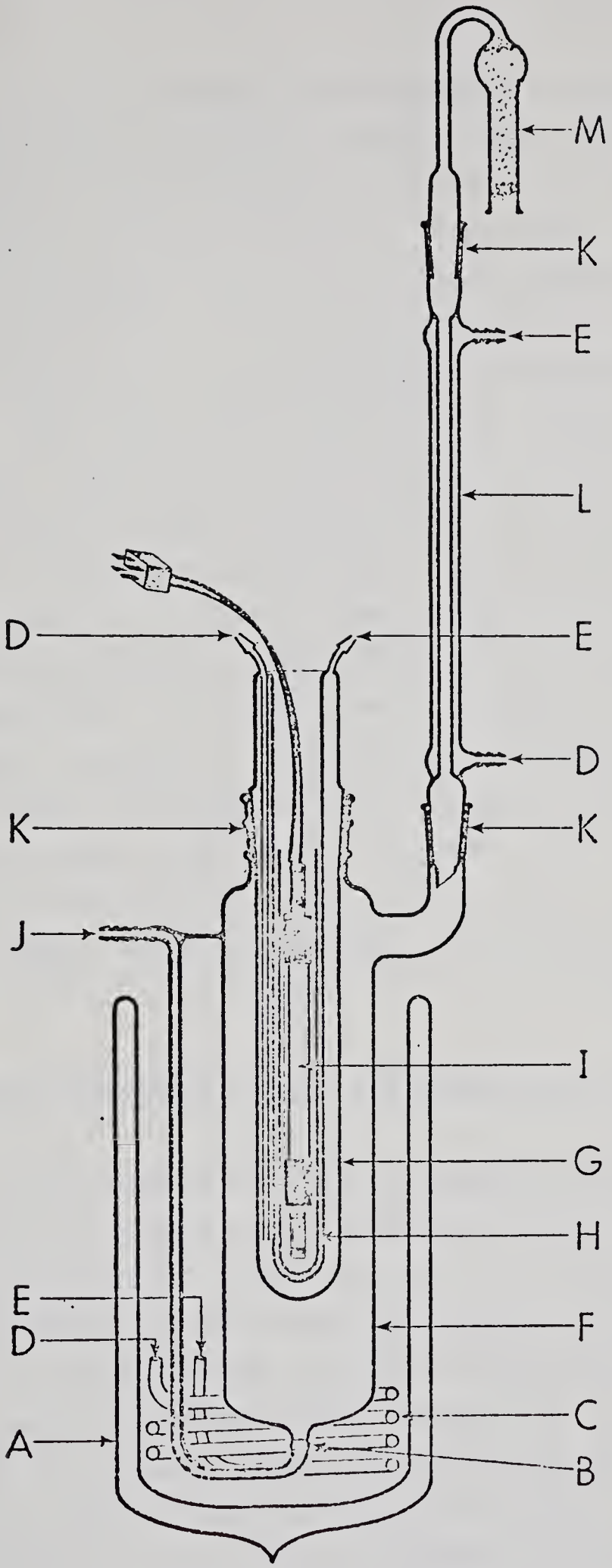

Fig. 1. A. Dewar flask; B. sintered glass filter; C. metal cooling coil; D. water inlet; E. water outlet; F. reaction vessel; G. quartz immersion well; H. pyrex filter; I. lamp; J. nitrogen gas inlet; K. ground glass joint; L. condenser; M. calcium chloride drying tube.

92 mmol) in 150 ml of ether at 0° and under a nitrogen atmosphere was added dropwise over a period of 30 min, 112 ml (179 mmol) of 1.8 M methyllithium. After stirring for an additional 30 min, a solution of photoadduct 3 (5.1 g; 28 mmol) in 50 of ether was added dropwise over a 30 min period. The reaction was maintained at 0° with stirring for an additional 2 hr. The resulting mixture was poured slowly into 2000 ml of vigorously stirred ice-cold 1 N hydrochloric acid and filtered. The filtrate was extracted with chloroform (3 x 500 ml). The combined organic extracts were washed with water (1000 ml) and saturated aqueous sodium chloride (1000 ml), dried over magnesium sulfate, filtered, and concentrated. The brown oil product was chromatographed on a Kiesegel column using a solution of 5% ether in benzene as eluent giving, in addition to 0.4 g (7%) of unreacted starting material, 3.4 g (67% based on consumed material) of 4 and 0.28 g (7%) of alcohol 5. Keto-acetate 4 showed the following spectral data: ir (film) ν 1743 cm^{-1} (ketone and ester); nmr (CCl_4) δ 0.83-1.19 (d's, 6 H, 2 CH_3-), 2.00 (s, 3 H, CH_3COO-) and 4.39-5.36 (m's, 1 H, -CHOCOCH$_3$); mass spectrum M^+ 196.1104 (Calcd for $C_{11}H_{16}O_3$: 196.1100).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 66.32; H, 8.22. Found: C, 66.77; H, 8.28.

6-Hydroxy-4,7-dimethylbicyclo[3.2.0]heptan-2-one (5)

To a solution of 1.7 g (8.5 mmol) of keto-acetate 4 in 15 ml of methanol was added 15 ml of saturated aqueous sodium carbonate. The resulting mixture, after stirring at room temperature for 5 hr, was diluted with 50 ml of water and continuously extracted with chloroform for 24 hr. The chloroform solution was dried with sodium sulfate, filtered and concentrated giving a yellow oil. Column chromatography of the oil on Kiesegel using a solution of 5% ether in benzene as eluent yielded 1 g (76%) of keto-alcohol 5: ir (film) ν 3440 (alcohol) and 1724 cm^{-1} (ketone); nmr (CCl_4) δ 0.98 and 1.16 (both d, total 3 H, J = 7 Hz, CH_3-), 1.09 and 1.19 (both d, total 3 H, J = 6 Hz, CH_3-), 3.25 (s, 1 H, -OH), and 3.57-4.18 (2 t and 1 d, 1 H, CHOH); mass spectrum M^+ 154.09930 (Calcd for $C_9H_{14}O_2$: 154.09938).

4,7-Dimethylbicyclo[3.2.0]heptan-6-ol (6)

A. Wolff-Kishner Reduction[15,16] of 5

To a stirred solution of 193 mg (1.25 mmol) of keto-alcohol 5 in 17 ml of triethylene glycol, were added 158 mg of potassium hydroxide and 0.22 ml (4.5 mmol) of 97% hydrazine. The mixture was heated at 110° for 1 hr, during that period water and low boiling material were removed from the mixture by means of exchanging condensers. The temperature was then raised to 190° and maintained at that temperature for 3.5 hr. The mixture was cooled to 0° and 50 ml of water was added. Extraction with chloroform (3 x 20 ml) followed by the usual work-up gave an oil which upon elution with 5% ether in benzene on a Kiesegel column gave 0.1 g (61%) of alcohol 6: ir (film) ν 3350 cm^{-1} (alcohol); nmr (CCl_4) δ 0.75-1.25 (d's, 3 H, 2 CH_3-), 3.20 (t, 1/2 H, J = 6 Hz, 1/2 -CHOH), and 3.67 (t and s, 1 1/2 H, -OH and 1/2 -CHOH); mass spectrum M^+ 140.

B. Via 4,7-Dimethylspiro[1',3'-dithiolane-2,2'-bicyclo[3.2.0]heptan-6-ol] (7)

To a solution of 1.8 g (12 mmol) of keto-alcohol 5 in 20 ml of 1,2-ethanedithiol was added 1.4 ml of boron trifluoride etherate. The reaction mixture after stirring at room temperature for 1.5 hr was poured into 500 ml of 4 N sodium hydroxide and extracted with chloroform (4 x 50 ml). The combined extracts were washed with 4 N sodium hydroxide (250 ml), water (250 ml) and saturated aqueous sodium chloride (250 ml), dried over magnesium sulfate, filtered, and concentrated. Column chromatography of the yellow oil on Kiesegel with 25% benzene in n-pentane as eluent yielded 2.3 g (86%0 of 7: ir (film) ν 3340 cm^{-1} (alcohol); nmr (CCl_4) δ 1.00-1.26 (d's, 6 H, 2 CH_3-), 3.19 (s, 4 H, $-SCH_2CH_2S-$) and 3.40-3.88 (d's 1 H, -CHOH); mass spectrum M^+ 230.0794 (Calcd for $C_{11}H_{18}S_2O$: 230.0800).

Anal. Calcd for $C_{11}H_{18}S_2O$: C, 57.35; H, 7.87; S, 27.83. Found: C, 57.28; H, 7.90; S, 27.72.

Thioketal 7 (1.9; 8.1 mmol) was dissolved in 100 ml of 95% ethanol and 20 g of W-2 Raney nickel[56] was added. The reaction mixture was refluxed for 24 hr, cooled to room temperature and filtered. Concentration of the filtrate gave an oil which was chromatographed on Kiesegel. Elution with a solution of 5% ether in benzene yielded 0.9 g (80%) of alcohol 6.

4,7-Dimethylbicyclo[3.2.0]heptan-6-one (8)

A. Jones Oxidation[17]

To a solution of 217 mg (1.6 mmol) of alcohol 6 in 2 ml of acetone at 0° was added 8 N Jones reagent until the orange color was retained (ca. 0.28 ml). The reaction mixture was stirred for an additional 5 min and 0.5 ml of isopropyl alcohol was added. The mixture was poured into 50 ml of water and extracted with methylene chloride (3 x 20 ml). The organic solution was dried over magnesium sulfate, filtered, and concentrated at 0° under aspirator pressure. The yellow oil was distilled using a Kugelrohr apparatus at an oven temperature of 55-60°/0.7 mm yielding 179 mg (≃83%) of ketone 8: ir (film) ν 1778 cm^{-1} (ketone); nmr (CCl_4) δ 0.86, 0.88, 0.92, and 1.02 (all d, total 6 H, 2 CH_3-); mass spectrum M^+138.10439 (Calcd for $C_9H_{14}O$: 138.10447); contaminated by a small amount of methylene chloride and acetone.

B. Modified Moffatt Oxidation[57]

At 0°, 1.45 g (10.4 mmol) of alcohol 6 was dissolved in 30 ml of freshly distilled dimethyl sulfoxide and 20 ml (210 mmol) of acetic anhydride was added. The resulting solution was allowed to stand at ≃3° for 48 hr and 25 ml of 10% sodium hydroxide was slowly added. The resulting mixture was extracted with methylene chloride (3 x 25 ml) and washed with 10% sodium hydroxide (3 x 25 ml) and water (100 ml). Drying ($MgSO_4$), filtration and concentration (at 0°) gave an oil which was distilled using a Kugelrohr apparatus at an oventemperature of 55-60°/0.7 mm yielding 1.26 g (≃88%) of ketone 8 (contaminated by

a small amount of methylene chloride and dimethyl sulfoxide).

3-Carbethoxy-4,8-dimethylbicyclo[3.3.0]octan-2-one (9)

Ketone 8 (269 mg; 2 mmol) was dissolved in 5 ml of anhydrous ether and cooled to -30° using a dry ice-acetone-carbon tetrachloride bath. A solution of 522 mg (3.9 mmol) of boron trifluoride etherate in 2 ml of ether was added dropwise over a 25 min period. After stirring for an additional 5 min 445 mg (3.9 mmol) of ethyl diazoacetate was added dropwise and the reaction mixture was stirred for 5 hr under an atmosphere of dry nitrogen. 10% aqueous sodium carbonate (5 ml) was then slowly added. The resulting mixture after its temperature was raised to 0° was diluted with 25 ml of water and extracted with methylene chloride (3 x 15 ml). Drying over magnesium sulfate, filtering and concentration gave an oily product which was chromatographed on Kiesegel using 25% benzene in n-pentane as eluent yielding 417 mg (93%) of keto-ester 9: ir (film) ν 3460 (enol), 1755 (ester), 1729 (ketone), 1658 (conjugated ester), and 1619 cm^{-1} (enol double bond); nmr (CCl_4) δ 0.99-1.09 (d's, 6 H, 2 CH_3-), 1.28 and 1.32 (both t, total 3 H, J = 7 Hz, $-CH_2\underline{CH_3}$), 4.12 and 4.14 (both q, total 2 H, J = 7 Hz, CH_3CH_2-), 4.28-4.53 (m, 1/2 H, -COCHCOO-), 10.43 and 10.55 (both s, 1/2 H, -C(OH)=C-); mass spectrum M^+ 224.1404 (Calcd for $C_{13}H_{20}O_3$: 224.1413).

4,8-Dimethylbicyclo[3.3.0]octan-2-one (10)

A solution of 78 mg (0.3 mmol) of keto-ester 9 in 2 ml of methanol and 2 ml of 10% aqueous sulfuric acid was refluxed under a nitrogen atmosphere for 24 hr. It was cooled to room temperature, diluted with 15 ml of water and extracted with methylene chloride (3 x 15 ml). The combined extracts were washed with water (15 ml), dried over magnesium sulfate, filtered, and concentrated at 0° under aspirator pressure. The residue was distilled using a Kugelrohr apparatus at an oven temperature of 45-50°/0.4 mm yielding 51 mg (96%) of ketone 10: ir (film) ν 1740 cm^{-1} (ketone); nmr (CCl_4) δ 1.03 and 1.04 (both d,

total 3 H, J = 5.5 Hz, CH_3-), 1.02 and 1.08 (both d, total 3 H, J = 7 Hz, CH_3-); mass spectrum M^+ 152.1194 (Calcd for $C_{10}H_{16}O$: 152.1186).

The 2,4-DNP derivative of the major isomer, mp 112-113° (95% ethanol) showed the following spectral data: ir (CCl_4) ν 3325 (NH), 1624 (C=N), 1596 and 1570 (aromatic), 1525 and 1345 cm^{-1} (NO_2); nmr (CCl_4) δ 1.08 (d, 3 H, J = 6 Hz, CH_3-), 1.22 (d, 3 H, J = 7 Hz, CH_3-), 7.85 (d, 1 H, J = 10 Hz, aromatic), 8.24 (dd, 1 H, J = 10 Hz, J' = 2 Hz, aromatic), and 9.02 (d, 1 H, J = 2 Hz, aromatic); mass spectrum M^+ 332.1479 (Calcd for $C_{16}H_{20}N_4O_4$: 332.1485).

4,8-Dimethylbicyclo[3.3.0]octan-1,3-d_3-2-one (11)

Keto-ester 9 (152 mg; 0.68 mmol) was treated under the same reaction conditions as described above, with deuterated sulfuric acid in deuterium oxide and methanol-d_4 to give deuterated ketone 11 (96 mg; 91%): ir (film) ν 1740 cm^{-1} (ketone); nmr (CCl_4) δ 1.03 (d, 3 H, J = 4 Hz, CH_3-), 1.06 (d, 3 H, J = 7 Hz, CH_3-); mass spectrum M^+ 155.1387 (Calcd for $C_{10}D_3H_{13}O$: 155.1314 [65.58%]) and 154.1320 (Calcd for $C_{10}D_2H_{14}O$: 154.1314 [9.05%]).

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